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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,292	07/09/2003	Ryuichi Morishita	Q75927	7040

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EXAMINER
HIRIYANNA, KELAGINAMANE T

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/615,292	MORISHITA ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/029,497.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/9,10/9, 2003 &* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction of invention

Applicant's election without traverse of restriction requirement in the reply filed on January 30, 2006 is acknowledged. Applicant elects without traverse the species restriction for further prosecution on merits.

Claims **7-9** are pending and presently under examination.

Specification

Priority

The Applicant has failed to identify the correct the date of filing of the priority document U.S. Application No. 09/029,497 in the filed transmittal letter. In addition, the preliminary amendment letter also supplied on the date of filing amends the specification to contain a proper reference to the above-listed Application and filing date, but fails to state the Patent number that issued from it, as well as the date of patenting. Lastly, the first paragraph amendment fails to list Application No. 09/660,552 and its status. Hence, the priority information needs correction to comply with the requirements of the USPTO.

Applicant's priority is objected to, but preliminarily considered as to intend (priority to US Applications 09/660,522 (as divisional parent), 09/029,497 (as continuation of parent to 09/660,522), and to PCT/JP96/02359 (as 371 parent to 09/029,497), and also to JP 07-245475 and JP 08-058467 as foreign priority parents to PCT/JP96/02359).

Applicant is required to amend the first page of the specification, or supply an application data sheet containing the proper priority information and dates.

Information Disclosure Statements

Applicant's information disclosure statements have been considered, and only the basis of the English translations provided for those citations that are written in foreign languages. In addition, many citations have been crossed-out. These citations were crossed out, even though considered, as indicated by the Examiner's initials in each citation, because either: (i) the citation is improper in its content (e.g., missing author

information), or (ii) because such citation is not a publically-available document, and therefore could not be listed on the front page of a patent that may issue.

If Applicant wishes such to placed on the front page of a patent, Applicant should submit proper citations and/or the availability document with English translation, where needed.

Drawings

The drawings are objected to because drawings 12-15 each contain two panels, and the brief description of the drawings does not allow the Artisan to determine which panel indicates what information. Furthermore, Figures 2-3 contain a pound sign (i.e., "#") and it is not clear what marking indicates from the brief description of the drawings.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 contains the limitation "the membrane of which may be further fused to attenuated Sendai virus particles". Such limitation, by using the term "may" makes it unclear if such limitation is meant to limit the claim or not. Hence, the claim is rejected for lack of clarity.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of gene therapy for treating restenosis

after percutaneous transluminal coronary angioplasty by inducing angiogenesis in heart, comprising administering by direct intra coronary injection into heart muscle of the subject a sendai virus (HVJ) liposome encapsulated plasmid vector comprising a mammalian hepatocyte growth factor (HGF) gene coding sequences operably linked to a constitutive promoter, and wherein further cells of the heart muscle express the HGF protein, which protein then acts to increase angiogenesis in the muscle to which the vector has been administered, does not reasonably provide enablement for therapy of any and or all cardiac diseases with any and/or all vectors, any and/or all promoters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims:

The scope of the invention encompasses treatment of any or/and all cardiac diseases in a subject, comprising administration any region intracoronarily, any expression vector containing any HGF gene and variants of the same. In the absence of representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable

and would require undue experimentation to practice the invention in its full scope. Applicants' attention is drawn to In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the number of claimed genus/ or species of expression vectors, sites of administration to a subject, and cardiac diseases whose treatments are successfully completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

***Guidance of the Specification and the Existence of Working Examples*:** Applicant's specification broadly describes treatment of many diseases by HGF (pp. 1-2), a description that HGF has short half-life in the blood (p. 2), and recognition that if HGF could be produced locally, the problems with its short half-life may be overcome. A Broad description of the HGF gene is then provided (p. 8), a description of treating various diseases by gene therapy (pp. 9-10), a description of liposomes and HVJ-liposomes (pp. 11-12), methods for introduction of the gene into the body (p. 12), types of viral vectors (pp. 12-13), methods of administration (p. 13), *in vivo* and *ex vivo* treatments (pp. 13-15), and predicted amounts of vector to administer (p. 15). However, given the state of the art, such broad guidance does not constitute the specific direction and guidance the artisan would require to reasonably predict that any tissue could be treated, that any other tissue than the tissue which is being injected with vector could be treated, that any vector could be used, or that any promoter could be used.

Applicant's examples demonstrate the making of HVJ-liposomes comprising a plasmid where HGF is under the control of the SRa (SRα) promoter in a pUC-plasmid vector (Examples, Materials and Methods), similar vectors that express TGF-beta (Comparative E xample 2), expression of HGF in rat coronary endothelial cells after HVJ-liposome transformation *in vitro* (Test Example 1-), demonstration that HGF causes proliferation of endothelial cells (Test Example 2), HGF expressed from vascular smooth

muscle cells (VSMC) causes endothelial cells to proliferate (Test example 3), and also works for rat coronary endothelial cells (Test example 4), mixed populations of VSMC expressing HGF and either human (Test Example 5) or rat (Test example 6) endothelial cells, causes growth of the endothelial cells, a demonstration that HGF does not cause VSMC proliferation (Test example 7), a demonstration that the HVJ-liposome expressing HGF causes blood vessel growth in rat coronary muscle (Example 8), and a demonstration that TGF-beta increases proliferation of cartilage cells in similar vectors (Example 9). However, given the lack of reasonable predictability in the art, even in the face of Applicant's disclosure, the Artisan would not reasonably predict that any vector could be used, that any tissue could be treated, that tissues not the muscle which is being administered the vector could be treated, or that any non-constitutive promoter could be used. Further the broad claim of treating all diseases of heart by providing HGF is not supported by the specification where it only describes angiogenesis in response to treatment and is not supported by the art. There are no reports in art regarding using HGF for treating all the heart diseases that includes ischemic heart diseases, diseases due to lipid metabolism defects and due to systemic and pulmonary hypertension etc. "Given the chronic nature, complex etiology, and multifactorial pathogenesis of cardiaovascular diseases, targeting a single gene, however attractive a candidate is, may prove to be inadequate therapeutically" (Khurana et al., 2001, Hypertension 38:1210-1216, P.1215, col.1, 2nd paragraph). Given the state of the art coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods of treating all heart diseases as claimed.

State of the Art, the Predictability of the Art: At about the effective filing date of the present application art is unpredictable with regard to methods of gene transfers in vivo using both viral and non-viral vectors, as has been claimed in the instant invention, art is still unpredictable with regard to efficacy, specificity and safety. For example Miller, et al. (1995) FASEB J. 9:190-99, acknowledges various vectors available, but teaches that "no single delivery system is likely to be universally appropriate." For instance, the requirements of gene therapy for cystic fibrosis are greatly different from those of cancer

(p. 190, first paragraph). "Once again, targeting at the level of the vector has not yet been particularly well developed; hence, liposome or viral-mediated delivery of the CFTR gene to airway epithelial cells of CF patients has relied largely on the **localized delivery** of the vectors directly to the affected tissues." (p.198, first paragraph, emphasis added). Moreover, it was demonstrated in later published art, that the HVJ-liposome encapsulating a plasmid for delivery of the HGF gene is used, rather than naked plasmid delivery, because of the greatly increased transformation efficiency, as evidenced by Taniyama, et al. (2001) Circulation, 104: 2344-50. Hence, the Artisan, before, and even after the date of invention, recognized that the type of vector was critical to the invention and demonstration of any single vector would not reasonably predict the use of any other vector. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of many therapeutic genes and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions etc., in vivo (Reviewed in Goncalves et al, Bioessays, 2005, 27: 506-517). In addition there exists an unpredictability about the degree to which a foreign gene or vector would interfere with cellular genetic material as observed in treatment of X-SCID patients " These serious adverse events presented as a leukemia-like syndrome were surprising since the risk of insertional oncogenesis was considered to be negligible based on previous trials and on the perceived, though not universally accepted, notion of random retroviral integration" (Goncalves, Bioessays, 2005, 27: 506-517, p. 514, col.2, 1st ¶). Because of the art, as shown above, does not disclose enough information to reasonably predict that any vector could be used, that any tissue could be treated by injection into any particular muscle, or that any promoter could be used, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Amount of experimentation necessary: Because of the lack of working examples, insufficient guidance and direction provided by Applicant, the inherent

unpredictability of the art, and the nature of the invention, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention in its full scope as claimed by Applicant. Such experimentation would be required to determine the types of vectors that could be used, the tissues that could be treated, and the types of promoters that would produce enough protein for a long enough period of time to effect treatment. Further these claims are not enabled because one of skilled in the art, at the date of filing, would not be able to rely upon the state of the art in order to successfully predict a priori the in vivo effects of claimed gene transfers in a subject. Accordingly, in view of the lack of teachings in the art or guidance provided by the specification with regard to an enabled use of a method for safe treatment of a disease or conditions of heart and in sufficient number of species as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of gene therapy for treating restenosis after percutaneous transluminal coronary angioplasty by inducing angiogenesis in heart, comprising administering by direct intra coronary injection into heart muscle of the subject a sendai virus (HVJ) liposome encapsulated plasmid vector comprising a mammalian hepatocyte growth factor (HGF) gene coding sequences operably linked to a constitutive promoter.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-**

0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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4/17/06